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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/633,093	08/04/2000	Joel S. Greenberger	07787-004003	2079

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EXAMINER

LI, QIAN JANICE

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/633,093

Applicant(s)

GREENBERGER ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-11, 21-28 and 30-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-28, 30 and 34 is/are rejected.
- 7) ☒ Claim(s) 2-11 and 31-33 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 August 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

The amendment filed 3/25/04 has been entered. Claims 1 and 29 have been canceled. Claims 32-34 are newly submitted. Currently, claims 2-11, 21-28, and 30-34 are pending and under examination.

Upon further consideration, new grounds of rejections are necessitated. Unless otherwise indicated, previous rejections that have been rendered moot in view of claim amendment, persuasive arguments, and new grounds of rejections will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is vague and indefinite because it is unclear what step of the method of claim 31 includes thawing BMSCs, thus the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 102/103

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21, 22, 24-27, and 34 are newly rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Greenberger et al* (EP 0 381 490 A2, 8-8-90).

These claims are drawn to a population of bone marrow stromal cells transfected with an exogenous gene, wherein the cells have undergone a freeze and thaw process (cryopreservation), and are currently in the thawed state, wherein the thawed BMSCs express the exogenous gene at a level at least about 77% of the level prior to the cryopreservation process.

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Greenberger et al teach human and mouse bone marrow stromal cells transfected with a foreign gene (abstract and examples), wherein the foreign gene encodes a secreted peptide such as clotting factor VIII and IX (e.g. pages 2 and 7), and TGF-alpha (page 6, lines 39-44); or a surface peptide such as EGF-receptor (page 6, lines 45-51).

It is noted that although the transfected cells disclosed by *Greenberger et al* did not go through a cryopreservation process, a BMSC in the thawed state has the same structure and functional feature as a BMSC that has never gone through the cryopreservation process. Although the specification indicates that some cells in the thawed BMSC population may have a lower transgene expression, the levels are no less than 77% compared to pre-cryopreservation. Such degree of variation could be expected in any cell population transfected with an exogenous gene including BMSCs (e.g. Ponnazhagan et al, J Virol 1997;71:8262-7, Valerio et al, Nucleic Acids Res. 1988;16:10083-97, and Graubert et al, Nucleic Acids Res. 1998;26:2849-58). The expression levels of the exogenous gene for the BMSCs disclosed by *Greenberger et al* would meet claim limitation because the cells have not been cryopreserved, the transgene expression would be at the level of pre-cryopreservation. Hence, the phenotype of the transfected BMSCs disclosed by *Greenberger et al* is indistinguishable from the instantly claimed BMSCs.

It is also noted that in this and the following rejections, the prior art BMSCs differ from the claimed BMSCs only by whether they have been cryopreserved or not. However, the cryopreservation process does not appear to change the basic structure

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and function of a transfected bone marrow stromal cell. The situation is analogous to the case law regarding the product-by-process claim, wherein the court rules patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Accordingly, *Greenberger et al* anticipate or in the alternative as obvious over the instant claims.

Claims 21, 23, 24-26, and 34 are newly rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Lozier et al* (Hum Gene Ther 1994).

These claims are drawn to a population of bone marrow stromal cells, preferably from canine and transfected with an exogenous gene, wherein the cells have undergone a freeze and thaw process, and are in the thawed state, wherein the thawed BMSCs express the exogenous gene at a level at least about 77% of the level prior to the cryopreservation process.

Lozier et al teach canine bone marrow stromal cells transfected with a foreign gene (e.g. page 318, left column), wherein the foreign gene encodes a secreted peptide-clotting factor IX.

It is noted that although the transfected cells disclosed by *Lozier et al* did not go through a cryopreservation process, a BMSC in the thawed state has the same structure and function as a BMSC that has never gone through the cryopreservation process. Although the specification indicates that some cells in the thawed BMSC population may have a lower transgene expression, the levels are no less than 77% compared to pre-cryopreservation. Such degree of variation could be expected in any cell population transfected with an exogenous gene including BMSCs. The expression levels of the exogenous gene would also meet claim limitation because it is at the level prior to cryopreservation. Hence, the structure and functional state of the transfected BMSCs disclose by *Lozier et al* are indistinguishable from the instantly claimed BMSCs.

Accordingly, *Lozier* anticipate or in the alternative as obvious over the instant claims.

Claims 21, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Greenberger et al* (EP 0 381 490 A2, 8-8-90), in view of *Newman et al* (US 6,020,188).

These claims are directed to transfected BMSCs expressing an exogenous gene, wherein the exogenous gene encodes an adhesion molecule, such as I-CAM.

The teaching of *Greenberger et al* has been discussed in detail above, particularly *Greenberger et al* teach transfected BMSCs expressing TGF- α or EGF-receptor that promote homing and engraftment of hematopoietic cells to the designated

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site of implant (lines 37-55, page 6). *Greenberger et al* do not teach the adhesion molecules as recited in claim 28.

Newman et al supplemented the teaching of *Greenberger et al* by illustrating that the adhesion molecules and their roles in various *in vivo* physiological processes are well known in the art at the time of the instant effective filing date. *Newman et al* teach polynucleotides encoding a cell surface adhesion molecule, specifically PECAM-1 (see abstract) and mammalian cells transduced by the polynucleotide (column 8, lines 9-16). *Newman et al* teach that well known CAMs also include N-CAM and ICAM (column 1, lines 48-65), and these molecules could be used for modulating leukocytes homing and angiogenic process (column 1, lines 49-65 and column 8, lines 51-58).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transducing the BMSCs as taught by *Greenberger et al* with a cell surface molecule such as CAMs as taught by *Newman et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because BMSCs expressing CAMs would also promote hematopoietic cell homing, and given the numerous homing molecules known in the art, these limitations fall within the bound of optimization for the reasonable skilled to select a gene of interest for expression in a cell population of interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

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Claims 21, 22, 24-27, and 34 are newly rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Greenberger et al* (US 5,849,287 or US 5,993,801 or US 6,258,354).

Greenberger et al teach bone marrow stromal cells transfected with a foreign gene (abstract and claims), wherein the foreign gene encodes a secreted peptide such as clotting factor VIII, and TGF- α ; or a surface peptide such as EGF-receptor (e.g. columns 7-8 of '287 patent).

It is noted that although the transfected cells disclosed by *Greenberger et al* did not go through a cryopreservation process, a BMSC in the thawed state has the same structure and functional feature as a BMSC that has never gone through the cryopreservation process. Although the specification indicates that some cells in the thawed BMSC population may have a lower transgene expression, the levels are no less than 77% compared to pre-cryopreservation. Such degree of variation could be expected in any cell population transfected with an exogenous gene including BMSCs. The expression levels of the exogenous gene would also meet claim limitation because it is at the level prior to cryopreservation. Hence, the transfected BMSCs disclosed by *Greenberger et al* are indistinguishable from the instantly claimed BMSCs.

Accordingly, *Greenberger et al* anticipate or in the alternative as obvious over the instant claims.

The above-applied references have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed

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subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Claims 21, 22, 24-27, and 34 are newly rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The claimed cells are disclosed in US 5,849,287 or US 5,993,801 or US 6,258,354 as discussed in detail in the immediate preceding rejection, yet the cited patents have different inventive entity with the present applicants. It is unclear who is the real inventor.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 21, 22, 24-27, and 34 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. US 5,849,287 or claims 1-19 of US 5,993,801 or claims 1-9 of US 6,258,354.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed subject matter is fully disclosed in the cited patents. The claims of the present application and the cited patents differ one from the other in that the claims of the cited patents are drawn to a method of using the transfected BMSCs encompassed by instantly claimed cells. However, there is no unobvious step in the process, and the method of using the transfected BMSCs flows directly from the intended use taught in the specification.

Accordingly, the claimed processes in the copending and the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claim Objections

Claim 31 is objected to because the pre-amble of the claim is directed to preserving any type of cells whereas the body of the claim is drawn to preserving BMSCs.

Claims 2-11, 32, 33 are objected to as being dependent upon an objected base claim, but would be allowable if the base claim is properly amended.

Conclusion

No claim is allowed. Claims 2-11, 31-33 appear to be free of the cited prior art of record. However, they are subject to objections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JANICE LI
PATENT EXAMINER



Q. Janice Li, M.D.
Primary Patent Examiner
Art Unit 1632



August 9, 2004